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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,328	12/07/1999	KUBER T. SAMPATH	CIBT-P01-514	9813
28120	7590	02/07/2006	EXAMINER	
FISH & NEAVE IP GROUP ROPES & GRAY LLP ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			ROMEO, DAVID S	
			ART UNIT	PAPER NUMBER
			1647	
DATE MAILED: 02/07/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 09/445,328	Applicant(s) SAMPATH ET AL	
	Examiner David S. Romeo	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 11/17/2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 2,5,6,8,9,11,12,14-38 and 53-59 is/are pending in the application.
- 4a) Of the above claim(s) 21,22,25 and 28-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2,5,6,8,9,11,12,14-20,23,24,26,27,35-38 and 53-59 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 2,5,6,8,9,11,12,14-38 and 53-59 are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                                                        |                                                                                         |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/2005 has been entered.

Claims 2, 5, 6, 8, 9, 11, 12, 14-38 and 53-59 are pending. Applicant's election with traverse of Group X, the species OP-1, the species the mature form of OP-1, the species pre-renal causes of acute renal failure, the species decreased cardiac output, and the species intravenous administration in the paper mailed 08/06/2002 is acknowledged. Claims 21, 22, 25 and 28-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper mailed 08/06/2002.

Applicant's election of GFR in the reply filed on 03/01/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 5, 6, 8, 9, 11, 12, 14-20, 23, 24, 26, 27, 35-38 and 53-59 are being examined only to the extent they read upon the elected invention and/or species.

**Maintained Formal Matters, Objections, and/or Rejections:**

***Claim Rejections - 35 USC § 103***

Claims 2, 5, 6, 8, 9, 11, 12, 14, 23, 24, 26, 27, 35, 36, 37, 38, 53, 56, 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93).

Claims 2, 15-20, 53, 54, 55, 58 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kuberasampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93) as applied to claims 2, 53 above, and further in view of Anderson (Chapter 275, in Harrison's Principles Of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles Of Internal Medicine, 1994).

Applicants argue that because TGF- $\beta$ 1, CsA and NSAIDs were known to be both (i) anti-inflammatory agents that inhibit ICAM adhesiveness and (ii) detrimental to renal function, skilled artisans would not have a reasonable expectation for improving renal function using OP-1 because skilled artisans would have expected OP-1 to have the same detrimental renal side-effects that TGF- $\beta$ 1, CsA, or NSAIDs have. Applicants' arguments have been fully considered but they are not persuasive. Applicants have not established a nexus between (i) and (ii). Nor have Applicants have established a causal relationship between (i) and (ii). Therefore, there is no evidence of record that OP-1 possesses any of the detrimental renal side-effects of TGF- $\beta$ 1, CsA, or NSAIDs or that one skilled in the art would have expected OP-1 to possess any of the detrimental renal side-effects of TGF- $\beta$ 1, CsA, or NSAIDs. If one is to accept Applicants' asserted connection between (i) and (ii), then one must also find persuasive the argument that if

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fifty percent of women who have breast cancer also have brown hair, then brown hair causes cancer. The weakness in Applicants' argument is insufficient to rebut the *prima facie* case of obviousness. The fact that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (Kelly, page 1062, left column, full paragraph 2), that Kelly suggests a critical role for leukocytes and adhesion molecules, in particular ICAM-1, in the pathophysiology of ischemic acute renal failure that may have important therapeutic implications for the treatment of acute renal failure in humans (page 1062, left column, full paragraph 3) and that Kuberasampath and Lefer teach that OP-1 is an agent that exhibits significant anti-adherent actions on PMNs provides one of ordinary skill in the art with at least a reasonable expectation of success.

Applicants argue that the examiner's reasoning is internally inconsistent. Applicant's arguments have been fully considered but they are not persuasive. Applicants are arguing that the properties of TGF- $\beta$ 1, CsA, and NSAIDs can be extrapolated to OP-1. However, Applicants' arguments are insufficient because Applicants have not established a nexus between (i) and (ii). Nor have Applicants established a causal relationship between (i) and (ii). Therefore, there is no evidence of record that that OP-1 possesses any of the detrimental renal side-effects of TGF- $\beta$ 1, CsA, or NSAIDs or that one skilled in the art would have expected OP-1 to possess any of the detrimental renal side-effects of TGF- $\beta$ 1, CsA, or NSAIDs. It is not a question of being internally inconsistent. The question is whether Applicants' evidence submitted is sufficient to rebut the *prima facie* case of obviousness. It is not. Accordingly, Applicants have not provided an expectation of failure for using OP-1 to treat ARF. The examiner is not demanding a higher burden of proof from Applicants. The examiner's position is that Applicants have presented

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insufficient evidence to rebut the *prima facie* case of obviousness. The examiner is unaware of any legal requirement that references must provide “experimental data that OP-1 improves renal function in ARF” in order to establish obviousness. In response to applicant's argument that none of the cited references provides experimental data that OP-1 improves renal function, the test for obviousness is not whether the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. The fact that agents designed to block leukocyte-endothelial interactions mediated via ICAM-1 may be therapeutically effective in the prevention and treatment of acute renal failure (Kelly, page 1062, left column, full paragraph 2), that Kelly suggests a critical role for leukocytes and adhesion molecules, in particular ICAM-1, in the pathophysiology of ischemic acute renal failure that may have important therapeutic implications for the treatment of acute renal failure in humans (page 1062, left column, full paragraph 3) and that Kuberasampath and Lefer teach that OP-1 is an agent that exhibits significant anti-adherent actions on PMNs provides a teaching, suggestion or motivation for one of ordinary skill in the art to use OP-1 in the prevention and treatment of acute renal failure.

Applicants argue that the examiner has not set forth how the references teach or suggest the improvement of a marker of renal function because “expectation of success” is not relevant to the requirement that the references teach or suggest all the claim limitations. Applicants’ arguments have been fully considered but they are not persuasive. Kelly shows an improvement of BUN and creatinine levels in ICAM-deficient mice after renal ischemia (page 1057, Figure 3). In addition, Kuberasampath teaches that OP-1 reduces or prevents the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, and also prevents or

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reduces the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades (page 38, line 3, through page 40, line 9), and that the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue (page 40, full paragraph 2). An improvement in a marker of renal function would have been obvious to one of ordinary skill in the art. That is to say, one of ordinary skill in the art would have a reasonable expectation of improving a marker of renal function. The fact that applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

Applicants argue that the examiner has failed to examine pre-renal causes of ARF. Applicants' arguments have been fully considered but they are not persuasive. The examiner made specific findings as to the elected species decreased cardiac output in the Office action mailed 07/12/2004 at page 10, last full paragraph and paragraph bridging pages 10-11.

Applicants argue that the examiner's *prima facie* case of obviousness only applies to ARF caused by renal ischemia. Applicants argue that renal ischemia and glomerulonephritis are intrinsic causes of renal failure, not pre-renal causes, as evidenced by the 2<sup>nd</sup> paragraph of the specification, Exhibit A and U. S. Patent No. 5,576,287. Applicants argue that the rationale for the rejection would not apply to pre-renal causes of ARF. Applicants argue that, unlike ischemia, pre-renal causes do not result in kidney tissue damage. Applicants argue that one of ordinary skill in the art would not be motivated to use OP-1 to treat ARF in the absence of kidney damage. Applicants' arguments have been fully considered but not only are they are not persuasive, they are wrong. Brady (Exhibit A, 11/17/2005) teaches that severe or prolonged

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hypoperfusion may lead to ischemic renal parenchymal injury and intrinsic renal azotemia (page 1266, left column, full paragraph 2). Applicants' arguments also contradict the specification. See page 1, lines 21-25, "Pre-renal causes ... may lead to significant permanent and/or progressive damage to renal tissues." Further, each of claims 2, 53 and 58 recite "a mammal afflicted with acute renal failure." Reciting "mammal is afflicted with a pre-renal cause of acute renal failure" (claim 20) or "the acute renal failure being one arising from a pre-renal cause" (claim 58) does not exclude kidney tissue damage. Therefore, Applicants' arguments are not persuasive.

### *Conclusion*

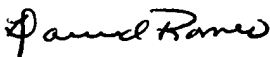
No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.



DAVID ROMEO  
PRIMARY EXAMINER  
ART UNIT 1647